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Toriello-Carey Syndrome: Evidence for X-Linked Inheritance

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Toriello-Carey syndrome is characterized by agenesis of the corpus callosum, telecanthus, short palpebral fissures, Robin sequence, abnormal ears, cardiac anomalies, and hypotonia. We describe two patients with Toriello-Carey syndrome and call attention to an unbalanced sex ratio. The first patient, a male, was born at term by Cesarean section and manifests micrognathia, cleft soft palate, hypoplastic right ear, anotia on the left side, cerebellar vermis hypoplasia, hydrocephalus, agenesis of the corpus callosum, and hypoplastic left heart. He died 2 days after birth. The second patient is the male sib of a patient reported previously [Am J Med Genet 42: 374–376; 1992]. He had large fontanelles, telecanthus, a short nose, small and malformed ears, micrognathia, a large ventricular septal defect, and pulmonary stenosis. At age 8 months he has growth retardation and developmental delay. A sister is unaffected. Review documented eight other patients with Toriello-Carey syndrome, six of whom were male. The two female patients are less severely affected and are still alive. Of the other male patients, all are deceased except one who is still alive at age 5 years; he has severe growth retardation (−3 SD), mental retardation (DQ44), severe speech delay, and characteristic anomalies. The predominance of affected males and the milder phenotype in the female patients suggests an X-linked gene or sex influenced gene.

KEY WORDS: agenesis of the corpus callosum, Robin sequence, cardiac defect, malformed ears, X-linked, developmental delay

INTRODUCTION

Toriello and Carey [1988] described four patients with multiple congenital anomalies including agenesis of the corpus callosum, Robin sequence, facial anomalies, hypotonia, and heart abnormalities. Sibs and both sexes were affected suggesting autosomal recessive inheritance. Since that time a total of eight patients, six of them male, have been reported [Lacombe et al., 1992; Jespers et al., 1993; Camera et al., 1993]. We report here two additional male patients diagnosed with Toriello-Carey syndrome and propose an X-linked mode of inheritance or sex influenced expression of the phenotype.

CLINICAL REPORTS

Patient 1

Patient 1 was born to a 31-year-old primigravida at 38 weeks gestation by Cesarean section because of prenatally diagnosed hydrocephalus. Birthweight was 2,557 g (25th centile), length was 51 cm (50th–75th centile), and head circumference (OFC) was 40.5 cm (>97th centile). Apgar scores were 4 and 6 at 1 and 5 min, respectively. There was a 2-vessel umbilical cord. The pregnancy was uncomplicated until 33 weeks of gestation when a breech presentation was suspected. Ultrasound examination at that time noted marked hydrocephalus and intrauterine growth retardation. An amniocentesis was performed. Chromosomes (at the 550 band level), alpha-fetoprotein, and acetylcholinesterase were normal. The family history was unremarkable. There was no consanguinity and no exposure to known teratogens.

At birth, the patient had a large round head, high forehead, prominent scalp veins, forehead hair extending to the eyebrows, no frontal bossing, anteverted nostrils, micrognathia (Fig. 1); cleft of the soft palate; hypoplastic right ear; anotia on the left side (Fig. 2); hypoplastic and dysplastic nails (Figs. 3, 4); and an undescended left testicle. A chest radiograph showed a left cervical rib and absent distal portion of the left 4th rib. Magnetic resonance imaging of the brain documented marked ventriculomegaly, cerebellar hypoplasia, Dandy-Walker malformation, and agenesis of the corpus callosum (Figs. 5, 6). An echocardiogram documented a complex hypoplastic left heart, atretic mitral

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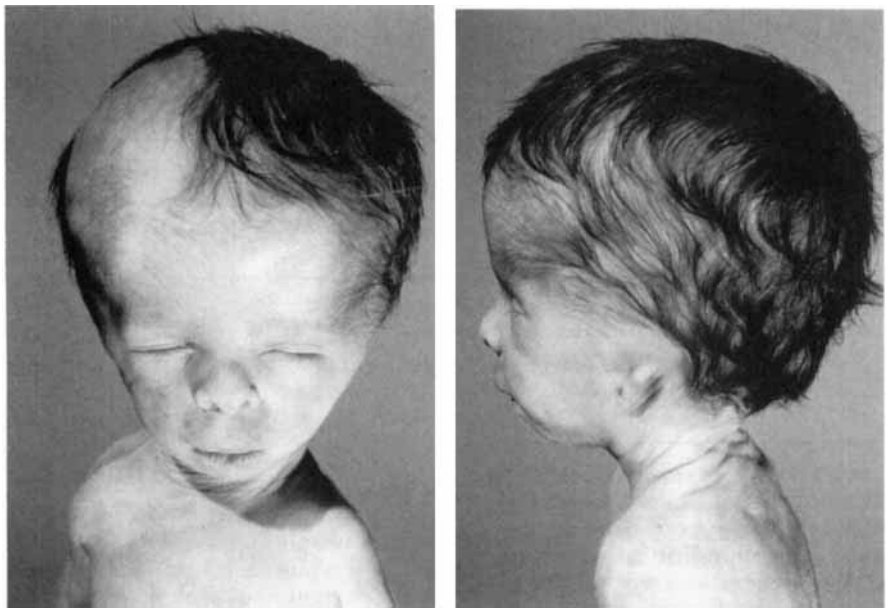
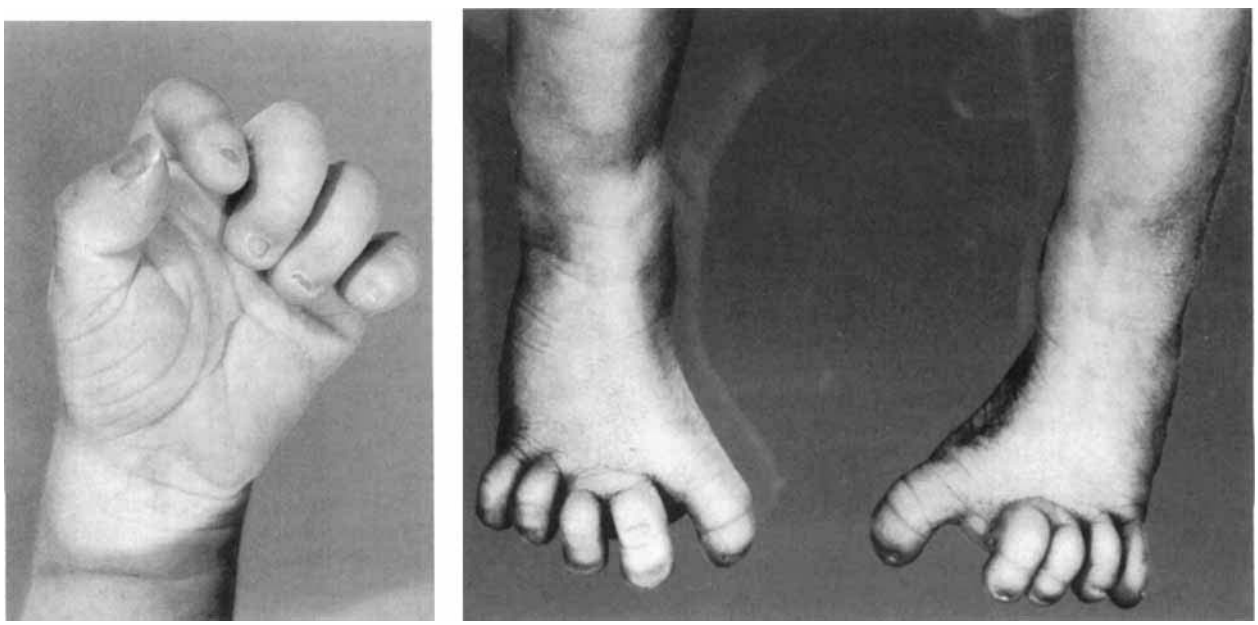


Figs. 1, 2. Patient 1, macrocephaly, short nose, micrognathia, telecanthus, excess neck skin, and left anotia.

valve, and a ventricular septal defect. The patient died on day 2 of life. An autopsy confirmed the above findings.

Patient 2

Patient 2 is the brother of a patient previously diagnosed with the Toriello-Carey syndrome and described by Lacombe et al. [1992]. There is a normal 7-year-old sister. He was born at term to a G3P3 female and a non-consanguineous male. Birthweight was 3150 g (25th centile), length was 50 cm (75th centile), and OFC was 35 cm (>75th centile). Apgar scores were 10 and 10, at 1 and 5 min, respectively. The abnormal physical findings were very large fontanelles; high forehead; hirsutism of the forehead; telecanthus; short nose; apparently low-set malformed ears, micrognathia, short neck, brachydactyly, and hypotonia (Figs. 7, 8). The palate was normal. There were no genital abnormali-



Figs. 3, 4. Patient 1, hypoplastic nails with unusual placement of the toes.

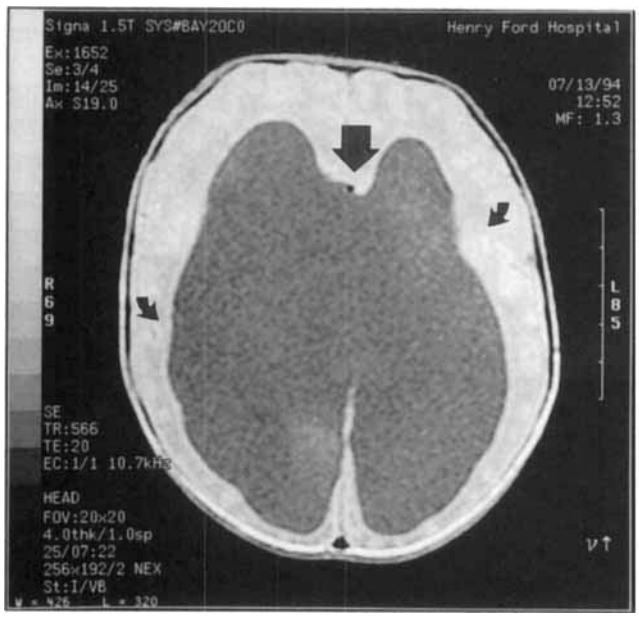


Fig. 5. Patient 1, MRI of the brain. The position of the anterior cerebral artery (large arrow) relative to the cerebral cortex indicates absence of the corpus callosum in spite of the marked dilatation of the lateral ventricles (small arrows). Dilatation of the lateral and third ventricles was due to aqueductal obstruction.

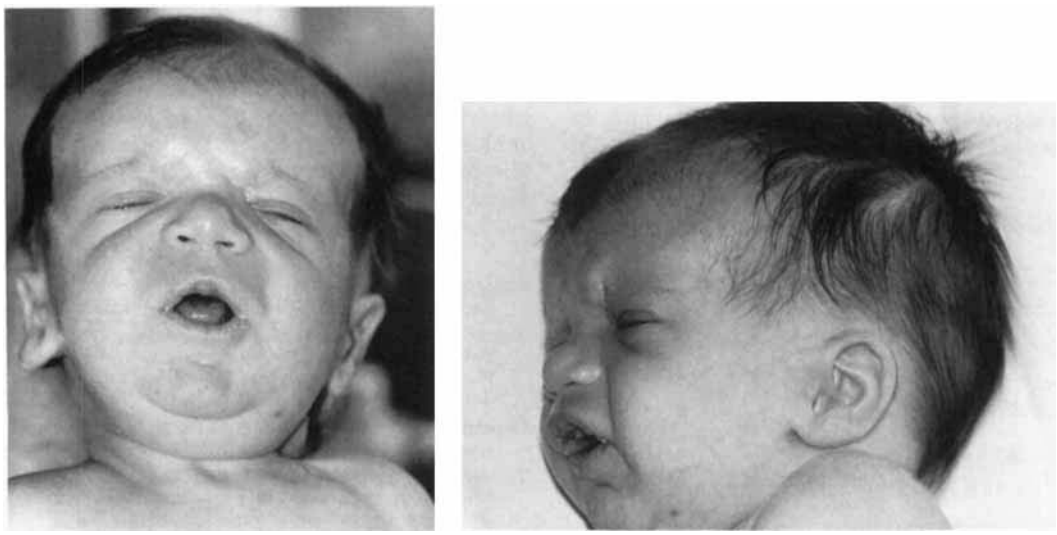
Fig. 6. Patient 1, MRI of the brain, note the arachnoid cyst in the posterior fossa.

ties. Ultrasound examination showed a large ventricular septal defect with pulmonary stenosis. A skeletal survey was normal. Chromosomes were normal. Cerebral ultrasound was normal without evidence of hydrocephalus or agenesis of the corpus callosum. Abdominal ultrasound showed renal asymmetry with a small right kidney.

At age 5 months the patient had growth retardation, weight was 5.9 kg (5th centile), length was 62 cm (5–10th centile), and OFC 44 cm (75th centile) with relative macrocephaly. At age 8 months, weight was 6.9 kg (5th centile), length was 66 cm (5–10th centile), and OFC was 46.3 cm (75th centile). He had a large anterior fontanelle, telecanthus, short palpebral fissures, depressed nasal bridge, microretrognathia, malocclusion, and hypotonia. He is developmentally delayed.

DISCUSSION

We describe two male patients with apparent Toriello-Carey syndrome. They have many of the classic findings of this condition including short palpebral fissures, telecanthus, short nose, micrognathia, malformed ears, cardiac defect, and hypotonia. One also



Figs. 7, 8. Patient 2, short nose, micrognathia, small mouth, telecanthus and possibly low-set ears.

TABLE I. Comparison of Cases 1 and 2 With Eight Others*

	Males					Females	
Characteristics	#1	#2	Toriello	Lacombe	Jespers	Toriello	Camera
Sex	M	M	3M	M	2M	F	F
Hydrocephalus	+	−	NR	−	NR	NR	NR
Large fontanelles	+	+	1/1	+	−	NR	+
Macrocephaly	+	+	−	+	+	−	−
Agenesis of corpus callosum	+	−	+	+	1/2	−	−
Vermis hypoplasia	+	−	NR	−	+	NR	NR
Short palpebral fissures	+	+	+	+	−	+	+
Hypertelorism/ telecanthus	+	+	+	+	+	+	+
Small/short nose	+	+	+	+	1/2	+	+
Micrognathia	+	+	+	+	+	+	+
Cleft palate	+	−	+	−	+	+	+
Malformed ears	+	+	1/2	+	+	+	+
Excess neck skin	+	−	1/1	−	+	+	−
Laryngeal/hypopharyngeal anomaly	NR	+	1/1	−	+	+	+
Cardiac defect	+	+	+	+(CM)	+	−	+
Hypotonia	+	+	+	+	+	+	+
Cryptorchidism	+	−	+	+	1/2	NA	NA
Dysplastic nails	+	−	1/3	−	1/2	−	−
Brachydactyly	NR	+	+	+	NR	+	−
Bone abnormalities	+	−	1/1	+	+	−	+
Postnatal growth retardation	NA	+	1/1	+	NA	+	+
Developmental delay	NA	+	1/1	+	NA	+	+
Omphalocele	−	−	−	−	+	−	−
Hirschsprung disease	−	−	−	−	+	−	−
Early infant death	+	−	+	−	+	−	−

* (+), present; (−), not present; NA, not applicable; NR, not reported; CM, cardiomyopathy; M, male; F, female.

had severe hydrocephalus, which has not previously been reported with this condition.

A review [Toriello and Carey, 1988; Lacombe et al., 1992; Jespers et al., 1993; Camera et al., 1993] showed eight additional cases of which six were male (Table I). The males appear to be more severely affected than the females (Table II). Of the eight male patients only two are still alive. All eight male patients had a congenital heart defect, as compared to only one of the females. Of the eight male patients, six had agenesis of the corpus callosum. The two female patients, who are both living, did not have agenesis of the corpus callosum and appear to have less delayed development than the affected males. Because of the preponderance of affected males and their more serious clinical course, we postulate X-linked inheritance. It is also possible that this may be inherited as an autosomal recessive condition with a sex influence. Studies are currently underway to evaluate several of the mothers of the reported cases for mild manifestations of Toriello-Carey syndrome to support an X-linked mode of inheritance.

TABLE II. Comparison of Male vs. Female Patients With Toriello-Carey Syndrome

Description	Males	Females
Number of individuals	8	2
Agenesis of the corpus callosum	6	0
Heart defect	8	1
Early infant death	6	0
Developmental delay	Moderate to severe	Mild to moderate

NOTE ADDED IN PROOF

After this work was finished, we became aware of the abstract by Le Merrer et al., of a case report of two females mildly affected with Toriello-Carey syndrome [Le Merrer M, Chauvet ML, Briard ML (1991): Am J Hum Genet 49:146].

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